# APPENDIX A

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# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Leonard W. KAPLAN et al.

Confirmation No.: 4115

Serial No.: 09/920,340

Group Art Unit: 1617

Filing Date: August 1, 2001

Examiner: Mojdeh BAHAR

Title: FORMULATIONS OF MOMETASONE AND A BRONCHODILATOR FOR PULMONARY ADMINISTRATION

## DECLARATION OF LEONARD W. KAPLAN, M.D. UNDER 37 C.F.R. § 1.132

**Mail Stop AF**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Leonard W. Kaplan, declare the following:

1. I am a medical doctor specializing in the area of allergy therapeutics and am one of the inventors of U.S. Patent Application Serial No. 09/920,340, which is identified above (hereinafter referred to as "the subject application").

2. I understand the subject application is under a final rejection. I have read the final Office Action of June 9, 2003; the cited Sequeira et al. patent, U.S. Patent No. 5,837,699; and the cited Maxair Physician's Desk Reference monograph, and understand the content of each document.

3. On Monday, July 21, 2003, I attended an Examiner Interview at the United States Patent and Trademark Office for this matter. In attendance at the interview were Examiner Mojdeh Bahar, my co-inventor Karl Weinrich, and my patent attorneys Dianne Reed and Karen Canaan. At this interview, the advantages and unique aspects of the invention were explained to the Examiner and it was agreed that I would provide the Examiner with additional information in the form of an inventor Declaration and supporting literature supporting the nonobviousness of the claimed invention.

4. The cited Sequeira et al. reference teaches a method of treating a corticosteroid-responsive disease (i.e., an allergic or inflammatory disease) of the upper or lower airway passages, such as rhinitis and asthma, respectively; the method involves at least once-a-day administration of aerosolized particles of mometasone furoate to the surface of the airway passages (cols. 2, 6, and 7, passim, see, e.g., col. 2, lines 20-26 and col. 7, lines 36-48). The mometasone furoate of Sequeira et al. is administered in a dosage unit of 0.01 to 500 mg (col. 6, line 49 to col. 5, line 17). Sequeira et al. also teaches that mometasone furoate may be administered by oral inhalation or intranasally to treat diseases of the upper or lower airway passages as monotherapy or as adjuvant therapy with, *inter alia,* bronchodilators such as albuterol or theophylline (col. 5, lines 5-15). Sequeira et al. does not teach the incorporation of a short-acting bronchodilator in its composition for the treatment of allergic and/or inflammatory diseases of the upper or lower airway passages.

5. The Maxair monograph teaches pirbuterol acetate in the form of an inhaler for the treatment of asthma and bronchospasms at a dosage of 200-400 μg/day. The monograph also teaches that the inhaler may be used concurrently with steroid therapy, but does not specify the steroid or any other aspect of a steroid/pirbuterol combination.

6. The Examiner contends that the teachings of Sequeira et al. in combination with the teachings of the Maxair monograph would lead one of ordinary skill in the art to the claimed invention.

7. In the Amendment filed on January 10, 2003, it was argued that the novelty of the claimed invention lies in the administration of the claimed combination in a *single formulation* (*see,* p.6, 3rd full para.). The Examiner did not accept this argument as persuasive on the theory that because a corticosteroid and a short-acting bronchodilator are both independently useful for the treatment of asthma and related illnesses, the administration of the two drugs in a single dosage form is an obvious modification. The Examiner's position does not take into consideration several critical aspects of the claimed invention, which are discussed *infra* and which demonstrate the nonobviousness of the claimed invention.

8. By addressing the following three issues, the nonobviousness of the claimed invention becomes apparent, the issues are: (i) the problems associated with patient compliance of long-term corticosteroid therapy; (ii) the disadvantages of administering a corticosteroid with a long-acting bronchodilator; (iii) the improved compliance and effectiveness of corticosteroid therapy when a

corticosteroid is administered simultaneously with a short-acting bronchodilator; and (iv) corticosteroids have never been administered simultaneously with short-acting bronchodilators.

9. **The problems associated with patient compliance:** When treating patients with mild persistent asthma symptoms, two medications are usually prescribed: a short-acting bronchodilator and a long-acting controller medication such as a corticosteroid. When taking these two medications in separate dosage units, the patients quickly realize that the short-acting bronchodilator (usually albuterol or pirbuterol) alleviates their cough, wheezing, and shortness of breath within a few minutes. Because the inhaled corticosteroid takes 24 to 72 hours to exert any effect, within a very short period of time, patients stop taking the corticosteroid, i.e., they become non-compliant. When asked by a physician why they stopped taking their medication, they will explain, or rather complain, that the inhaled steroid did nothing to alleviate their asthma symptoms. Thus, patients become non-compliant to the corticosteroid therapy because the corticosteroid does not provide them with immediate relief of their symptoms. Once the patient has stopped using the inhaled corticosteroid, the patient's coughing, wheezing, and shortness of breath is soon exacerbated and the patient must return to the physician's office for additional treatment.

10. **The disadvantages of administering corticosteroids with long-acting bronchodilators:** The Advair® inhaler is a commercially available inhaler for use by asthma patients that combines in a single formulation a corticosteroid (fluticasone propionate) with a long-acting bronchodilator (salmeterol). There are several disadvantages to using this drug combination. First, because the bronchodilator is a long-acting bronchodilator, it takes from 30 to 45 minutes to begin working; thus, in order to have immediate relief from the onset of asthma symptoms, the patient must carry a rescue inhaler housing a short-acting bronchodilator (such as albuterol or pirbuterol). Second, when a patient self-administers the short-acting bronchodilator upon the onset of an asthma attack, upon relief of the symptoms, the patient has little incentive to self-administer the Advair combination. Third, because Advair inhaler only comes in fixed combinations of dosages, it is impossible for a patient to titrate the exact amount of corticosteroid that is necessary to suppress the airway inflammation that the patient is experiencing. In order to change the amount of corticosteroid to be administered to the patient, a new inhaler is necessary. The foregoing demonstrates that the addition of a long-acting bronchodilator to a corticosteroid as well as the use of rescue inhalers housing a short-term bronchodilator have failed to improve patient compliance with long-term corticosteroid therapy.

11. **Improving compliance:** One way to deal with patient non-compliance to corticosteroid therapy is to have the orally inhaled corticosteroid administered simultaneously with a short-acting bronchodilator. There are several advantages to this combination. The first advantage is that because the patient obtains immediate relief from symptoms of coughing, wheezing, and shortness of breath, the patient is encouraged to continue to take the combination every four hours or on an as-needed basis. Thus, the patient will self-administer the claimed formulation as if it is a short-acting bronchodilator and in so doing, will receive the benefits of the corticosteroid and experience none of the compliance problems associated with the latter. The second advantage is that the patient can titrate the exact amount of corticosteroid necessary to control the asthma symptoms. In other words, because the severity of the patient's symptoms dictates the amount of medication (form either the bronchodilator or the corticosteroid) that the patient self-administers, the patient will not overmedicate by taking the medication when no symptoms are apparent or undermedicate with a combination that fails to alleviate the symptoms. The third advantage is that the patient need only carry one inhaler on his or her person rather than two. On this latter point, it is noted that because the use of two inhalers gives a patient the illusion of overmedicating, a patient will be prone to resist using a second inhaler. By administering the corticosteroid and a short-acting bronchodilator in one single formulation, the patient will be predisposed to comply with the therapy.

12. **The claimed combination has never been considered:** While corticosteroids have been administered sequentially after the administration of a short-acting bronchodilator, the two drugs have never been administered simultaneously in a single formulation. The attached *Guidelines for the Diagnosis and Management of Asthma,* NIH Publication No. 97-4051 (July 1997) ("Guidelines") demonstrate that the separation of long-term asthma medications from quick relief medications is accepted within the allergy therapeutics community. Specifically, the table at pages 84 and 85 of the Guidelines shows that medications used for long-term control of asthma are categorically separated from medications used for quick relief of asthma. The reason for the categorical separation of long-term medications from quick-relief medications is explained on page 59 of the Guidelines with the following statement:

> Asthma medications are...categorized into two general classes: long term control medications taken daily on a long-term basis to achieve and maintain control of persistent asthma...and quick relief medications taken to provide prompt reversal of acute airflow obstruction and relief of accompanying bronchoconstriction. Patients with persistent asthma require both classes of medication.

The accepted principle that medications for long-term relief of asthma are separate from those for quick relief of asthma is the result of accepted notions that asthma is a two-part process consisting of airway inflammation and bronchospasm or bronchoconstriction (*see,* Guidelines, pp.8-9; p.9 Fig. 2; and p.10 col.2 to p.11 col.1). Nowhere in the Guidelines is it taught or suggested that medications used for long-term treatment of asthma may be combined with medications used for quick relief of asthma. Further, there is no indication in other literature that I have studied that suggests that such a combination is used for the treatment of asthma or other diseases of the upper and lower respiratory airways.

13. The invention described in the subject application is not obvious because it takes a new approach to the treatment in contravention of the accepted practices of allergy therapeutics.

14. I declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true and that all statements herein were made with full knowledge that willful false statements may jeopardize the validity of the subject patent application and any patent issuing therefrom and are punishable by fine, imprisonment, or both under Section 1001 of Title 18 of the United States Code.

Dated: 2 Sept 2003

By: Leonard W. Kaplan M.D.
Leonard W. Kaplan, M.D.